Research Article / Araştırma Makalesi

May Recovered COVID-19 Patients Have Impaired Myocardial Work?

İyileşen COVID-19 Hastalarında Miyokard Çalışması Bozulmuş Olabilir mi?

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Abstract

Background: The aim of this study was to investigate whether there are sequelae in left ventricular (LV) systolic function by comparing LV function in fully recovered COVID-19 patients with pulmonary involvement and healthy controls without COVID-19 by conventional echocardiography and myocardial work.
Materials and Methods: 55 healthy volunteers and 61 patients hospitalized with COVID-19 with pulmonary involvement were included. Patients did not need non-invasive or invasive mechanical ventilation support during hospitalization. Patients were included in the study if they were asymptomatic for at least six months after recovery from COVID-19. Transthoracic echocardiography (TTE) was performed. Demographic and clinical characteristics and laboratory test results were collected. Clinical characteristics, blood tests, TTE, speckle-tracking echocardiography (STE) and myocardial work results were compared.
Results: No statistically significant differences were found in the longitudinal strain parameters of the LV among the study groups. The patient group exhibited notably reduced levels of global work index (GWI), global constructed work (GCW), and global work efficiency (GWE). The patient group exhibited a notably elevated global wasted work (GWW).
Conclusions: The group of fully recovered asymptomatic COVID-19 patients with pulmonary involvement showed significantly lower values for GWI, GCW, and GWE, while GWW showed a significantly higher value. Myocardial work parameters may be useful in determining myocardial sequelae.

Key Words: COVID-19, Myocardial Work, Longitudinal strain, Speckle-tracking echocardiography

Öz

Amaç: Bu çalışmanın amacı tamamen iyileşmiş akciğer tutulumlu COVID-19 hastalarında sol ventrikül (LV) sistolik fonksiyonunda sekel olup olmadığını, COVID-19 geçirmemiş sağlıklı kontrol grubundaki kişilerle geleneksel ekokardiyografi ve miyokard çalışması ile karşılaştırarak incelemektir.
Materyal ve Metod: 55 sağlıklı gönüllü ve akciğer tutulumlu COVID-19 nedeniyle hastaneye yatışı yapılan 61 hasta dahil edildi. Hastaların hastanede yatışları sırasında non-invaziv veya invaziv mekanik ventilasyon desteğine ihtiyaçları olmadı. Hastalar COVID-19'dan iyileştikten sonra en az altı ay süreyle semptomsuzlarsa çalışmaya dahil edildi. Transtorasik ekokardiyografi (TTE) yapıldı. Demografik ve klinik özellikler ile laboratuvar test sonuçları toplandı. Klinik özellikler, kan testleri, TTE, STE ve miyokardiyal çalışma sonuçları karşılaştırıldı.
Bulgular: Çalışma grupları arasında LV'nin strain parametrelerinde istatistiksel olarak anlamlı bir fark bulunmadı. Hasta grubunda global çalışma indeksi (GWI), global yapılandırılmış çalışma (GCW) ve global çalışma verimliliği (GWE) düzeylerinde belirgin derecede azalma izlendi. (tüm p değerleri < 0.001) Hasta grubunda anlamlı derecede yüksek global boşa giden çalışma (GWW) düzeyi izlendi. (p=0.009)
Sonuç: Tamamen iyileşmiş, semptomsuz akciğer tutulumlu COVID-19 hastalarında GWI, GCW ve GWE anlamlı olarak düşük değerler gösterirken, GWW anlamlı olarak daha yüksek değerler gösterdi. Miyokardiyal çalışma parametreleri miyokardiyal sekelleri belirlemede yararlı olabilir.

Anahtar Kelimeler: COVID-19, Miyokardial iş, Uzunlamasına zorlanma, Benek izleme ekokardiyografi

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Introduction

The emergence of the coronavirus disease-2019 (COVID-19) on a global scale has led to a pandemic that has had a widespread impact on all nations, resulting in substantial rates of morbidity and mortality on a global scale (1). Today, variants emerging in different parts of the world are causing outbreaks and causing concerns about whether it will lead to a worldwide lockdown again (2). While previous research has demonstrated the existence of myocardial injury in patients with COVID-19 and its correlation with mortality (3, 4), there is a scarcity of data regarding the persistence of myocardial sequelae in patients recovered from COVID-19.

There are several cardiac presentations in COVID-19, such as acute myocardial infarction, myocarditis, acute heart failure, malignant arrhythmias, and pulmonary thromboembolism (5, 6). Approximately 8% of COVID-19 patients were found to have cardiac injury (7). The pathogenesis of myocardial injury is not fully understood, but theories include viral replication within cardiomyocytes (8), a direct role for the angiotensin converting enzyme 2 receptor (9), hypoxia due to pulmonary involvement (10), and a cytokine storm (10). Transthoracic echocardiography (TTE) is the primary method used to assess the systolic function of the left ventricle (LV). Despite its numerous limitations, such as interobserver variability and the inability to detect early abnormalities in left ventricular systolic function, left ventricular ejection fraction (LVEF) continues to be the predominant parameter utilized for evaluating systolic function (11, 12). Echocardiography is constantly advancing through the development of advancements in hardware and software systems. Two-dimensional (2D) speckle-tracking echocardiography (STE) has been developed to offer precise and consistent evaluation of myocardial function, with reduced angle and operator dependency. Due to its ability to detect subclinical impairment of cardiac function even when LVEF is in the normal range (13, 14), 2D STE has been widely used to investigate LV function in various diseases (15-18). However, it is limited by its load dependence. Increased afterload may decrease global longitudinal strain (GLS) and may cause inaccurate conclusions about LV systolic function (19). Another recent echocardiographic technique, myocardial work (MW), has appeared to provide a non-invasive measure of the LV pressure-strain relationship. Myocardial work assesses LV performance and incorporates afterload determination using blood pressure, providing a more load-independent measure compared to GLS (12, 20, 21).

In this study, it was investigated whether there are sequelae in LV systolic function by comparing LV function in fully recovered COVID-19 patients with pulmonary involvement and healthy controls without COVID-19 by conventional TTE and myocardial work.

Materials and Methods

It is a prospective observational cohort study of 55 healthy volunteers and 61 patients diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by reverse transcription-polymerase chain reaction from upper respiratory tract swabs. The participants had no history of chronic diseases. The control group was selected from volunteers who applied to the cardiology outpatient clinic for a check-up examination, had no complaints, had no known chronic disease and agreed to participate in the study. The patients had been hospitalized with COVID-19 with pulmonary involvement. Patients did not require non-invasive or invasive mechanical ventilation support. Patients had negative smear test results at the end of the isolation period. Patients were included in the study if they were asymptomatic for at least six months after recovery from COVID-19. After the patients were included in the study, transthoracic echocardiography (TTE) was performed, and demographic and clinical characteristics and laboratory test results were collected. Clinical characteristics, blood tests, TTE, STE and myocardial work results were compared. The ethics committee approved the study. All participants gave informed consent.

Echocardiography

TTE was done with a GE Vivid E95 echocardiography device (GE Healthcare; Vingmed Ultrasound, Horten, Norway) with an M5S probe (frequency range: 1.5-4.6 MHz). A single lead rhythm was recorded during the examination. Non-invasive measurement of blood pressure using a cuff was used in the MW calculation. Conventional echocardiographic parameters were obtained according to the recent recommendations (22). LVEF calculation was performed using a modified biplane Simpson technique. LV systolic strain parameters were calculated using EchoPAC version 202. The semi-automated Autostrain 3P endocardial boundary tracking approach was used to calculate global longitudinal strain (GLS) from the apical 4-chamber, apical 2-chamber and apical long-axis views. If LV endocardial boundaries were insufficient for assessment, manual adjustments were made. A bull's eye plot was then generated to show the global MW index and global LV work efficiency for all seventeen segments and all MW component values. The application also displayed a pressure-strain loop characterized by a global work index (GWI) equivalent to the LV GWI. The screen shows all the MW values and bars illustrating the correlation between constructive and wasted work, both on a global and segmental scale. After completing the main steps, the variables GWI, global work efficiency (GWE), global wasted work (GWW), and global constructed work (GCW) were automatically calculated (Figure 1).

Statistical Analysis

IBM SPSS Statistics 22 for Windows was utilized for data analysis. The nominal variables were expressed in numerical form and expressed as percentages. Continuous variables were represented using the mean and standard deviation (SD). The median and interquartile range were used to

represent variables that did not follow a normal distribution. The chi-squared test or Fisher's exact test was used to compare nominal variables. The Student's t-test was employed for continuous parametric variables. To compare continuous non-parametric variables, the Mann-Whitney U test was utilized. A p-value below 0.05 was considered to be a statistically significant result.

Results

The study enrolled 61 patients and 55 healthy volunteers. Table 1 displays the baseline characteristics and laboratory results of the study group. The study groups exhibited similar baseline characteristics and laboratory results.

Table 2 presents the echocardiographic findings of the study cohorts. The patient group exhibited a significantly larger left ventricular end-systolic diameter (LVESD) (30.52 ± 2.57 vs 27.40 ± 3.00, p<0.001). The other 2D TTE parameters were comparable between the study groups. There were no significant differences observed in the longitudinal strain parameters of the study groups. The patient group exhibited significantly lower levels of GWI (1584 (1481-2017) vs 2406 (2270-2540), p<0.001), GCW (2305 (1889-2526) vs 2719 (2604-2885), p=0.009), and GWE (88 (85-92) vs 93 (91-94) respectively, p<0.001). The patient group exhibited a significantly higher GWW (223 (215-353) vs 213 (203-226), p<0.001).

Table 1. Clinical characteristics of the patients, and laboratory data

	Patient group (n=61)	Control group (n=55)	p value
Patient characteristics			
Age (years)	41.6 ± 10.3	42.0 ± 9.9	0.809
Gender			0.318
Male (n, %)	39 (72.2%)	34 (61.8%)	
Female (n, %)	15 (27.8%)	21 (38.2%)	
BMI (kg/m^2)	25.92 ± 2.72	26.1 ± 4.34	0.444
Systolic blood pressure (mmHg)	116.5 ± 13.3	119.5 ± 10.6	0.198
Diastolic blood pressure (mmHg)	75.0 ± 7.2	76.8 ± 7.4	0.340
Laboratory Data			
Hemoglobin, g/dL	14.3 ± 1.2	13.7 ± 1.4	0.068
White blood cell count (10^3/µl)	7.1 ± 1.5	7.5 ± 3.3	0.423
Serum creatinine (mg/dL)	0.80 ± 0.05	0.80 ± 0.14	0.219
Glucose (mg/dL)	97.0 ± 25.6	105.6 ± 21.1	0.659
Sodium (mEq/L)	139.3 ± 2.2	136.4 ± 1.5	0.155
AST (unit/L)	21.0 ± 7.5	23.9 ± 7.9	0.259
ALT (unit/L)	24.2 ± 12.8	25.3 ± 8.7	0.130
Thyroid stimulating hormone (TSH) (mIU/L)	1.6 ± 1.3	1.6 ± 0.7	0.999

BMI, body mass index

Table 2. Echocardiography results

	Patient group (n=61)	Control group (n=55)	p value
LVEDD (mm)	45.4 ± 3.3	45.3 ± 2.9	0.890
LVESD (mm)	30.52 ± 2.57	27.40 ± 3.00	<0.001
LAV max	40.7 ± 10.1	38.8 ± 9.6	0.288
LVEF (%)	59.8 ± 9.4	61.2 ± 4.2	0.261
IVS (mm)	10.0 ± 1.1	9.2 ± 0.9	0.378
E/A ratio	1.1 ± 0.5	1.1 ± 0.3	0.665
Em lateral (cm/s)	0.15 ± 0.04	0.18 ± 0.02	0.074
Am lateral (cm/s)	0.12 ± 0.04	0.14 ± 0.13	0.197
TAPSE (mm)	23.4 ± 3.4	24.1 ± 3.2	0.091
LV-LS 4 chamber (%)	19.60 (19.00 - 20.47)	19.10 (18.00 - 20.05)	0.051
LV-LS 2 chamber (%)	21.63 (20.00 - 22.10)	21.10 (19.30 - 23.00)	0.767
LV-LS 3 chamber (%)	18.17 (18.00 - 21.30)	19.60 (18.10 - 21.70)	0.400
LV-GLS (%)	20.00 (20.00 - 20.00)	20.17 (18.71 - 20.92)	0.923
GWI (%mmHg)	1584 (1481 - 2017)	2406 (2270 - 2540)	<0.001
GCW (%mmHg)	2305 (1889 - 2526)	2719 (2604 - 2885)	<0.001
GWW (%mmHg)	223 (215 - 353)	213 (203 - 226)	0.009
GWE (%mmHg)	88 (85 - 92)	93 (91 - 94)	<0.001

LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAV max, left atrium maximum volume; LVEF, left ventricular ejection fraction; IVS, interventricular septum thickness; E, mitral inflow early diastolic velocity; A, mitral inflow late diastolic velocity; Em, mitral inflow early diastolic tissue velocity; Am, mitral inflow late diastolic tissue velocity; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricle; LS, longitudinal strain; GLS, global longitudinal strain; GWI, global work index; GCW global constructed work; GWW, global wasted work; GWE, global work efficiency

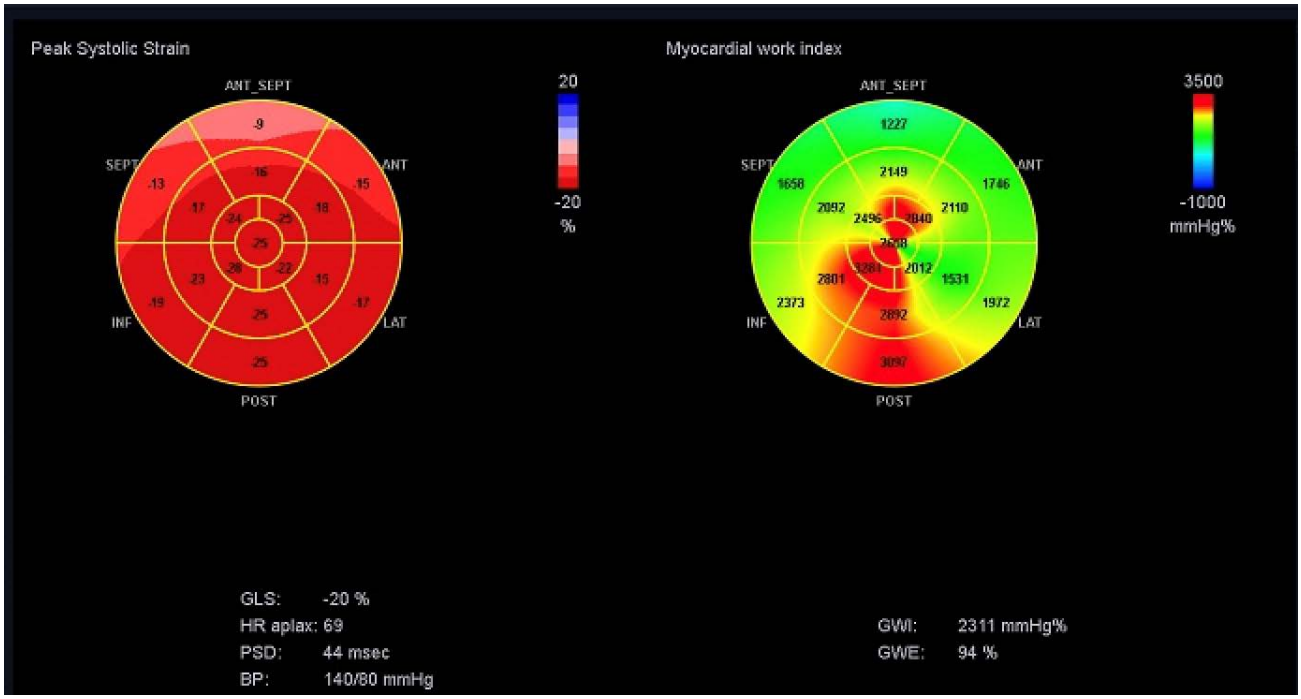

Figure 1. A 43-year-old male patient with healed COVID-19 underwent echocardiographic examination. A bulls-eye plot of global myocardial work index and global left ventricular work efficiency for all 17 segments is shown.

Discussion

New variants of COVID-19 emerging in different parts of the world continue to have a negative impact on human and public health. Today, we have a lot of information about the acute course of the disease and the cardiovascular (CV) complications it can cause, and we know that higher morbidity and mortality rates are seen in patients with CV complications. (23-26). Direct effects of the virus on the cell with angiotensin converting enzyme 2 (ACE-2), indirect effects of the virus with severe cytokine release and cytokine storm, respiratory failure inducing hypoxic injury, and atherosclerotic plaque complications (such as plaque rupture) have been shown as potential mechanisms of myocardial injury (27, 28). However, our knowledge of whether the myocardial damage that can develop in the course of COVID-19 leaves myocardial sequelae after the disease has healed is limited.

Our study included 61 patients with COVID-19 pneumonia who did not require intensive care or non-invasive mechanical ventilation support and a control group of 55 healthy volunteers without COVID-19.

The study comprised a cohort of 61 individuals diagnosed with COVID-19 pneumonia who did not necessitate intensive care or non-invasive mechanical ventilation assistance. Additionally, a control group consisting of 55 healthy volunteers without COVID-19 was included in the study. The patients did not have overt myocarditis. Patients were enrolled six months after healing from COVID-19. Participants were assessed by conventional TTE and STE. Our study demonstrated for the first time that LV myocardial work parameters were impaired six months after recovery from COVID-19 pneumonia, although there were no significant changes in conventional TTE parameters. Myocardial work may be of greater importance in the assessment of myocardial sequelae after COVID-19 pneumonia.

TTE is a cheap, rapid and widely available method of assessing cardiac function. LVEF is widely employed as the primary conventional metric for assessing left ventricular systolic function. However, LVEF is not sufficient to detect subclinical changes in many heart diseases (12, 29). Therefore, new echocardiographic techniques have been developed. GLS is one of the alternative parameters that have been developed to assess LV systolic function. The fact that GLS has lower inter- and intra-observer variability and can detect very mild LV systolic function changes before LVEF deteriorates in many cardiac diseases has increased its usefulness in clinical practice in recent years. However, the fact that GLS, like LVEF, is load dependent and can be affected by changes in pre- or afer-load (12, 14, 30, 31).

A recent study followed 42 individuals who had recovered from COVID-19 but still had symptoms and 42 healthy individuals for a median of 112 days. The patient group showed a significant reduction in LV-GLS regardless of comorbidities. Both hospitalized and non-hospitalized patients exhibited impaired LV strain, indicating these changes are not related to COVID-19 severity. (32) Another study with 214 hospitalized COVID-19 patients and 214 controls also found a significant decrease in LV-GLS, even after adjusting for cardiac risk factors, and linked LV-GLS to mortality. (33) The studies revealed a notable decrease in LV-GLS levels among the patient group, although the values fell within the normal range. (31, 32). In our study, 6 months after recovery

from COVID-19 pneumonia, there were no significant differences in LV longitudinal strain parameters between the study groups. The fact that LV-GLS remains within the normal range prevents it from being used in the echocardiographic assessment of any sequelae that may develop in the myocardium.

Myocardial work obtained by 2D-STE is a novel parameter for non-invasive assessment of the LV pressure-strain relationship and LV myocardial performance. It examines the impact of afterload and myocardial deformation on left ventricular systolic function. Recent studies have proposed the utilization of myocardial work in different cardiac diseases because of its reduced load dependence and consequently greater sensitivity in identifying subclinical myocardial dysfunction compared to LVEF and GLS alone (12, 20, 34). A study of 249 COVID-19 patients showed that elevated troponin levels were linked to a significant decrease in GWI, which correlated with higher oxygen demand and mortality. (35) Another study followed 66 individuals without prior cardiopulmonary conditions for one year post-COVID-19 recovery. Among them, 24 experienced dyspnea. While LVEF was similar between those with and without dyspnea, the dyspnea group had lower GCW and GWI, indicating an inverse relationship between these parameters and dyspnea. (36) In this study, it is demonstrated that GWI, GCW and GWE were significantly lower in the patient group, and GWW was significantly higher in the patient group. These findings in our study suggest that although overt myocarditis does not develop during the course of COVID-19 pneumonia, subclinical sequelae changes may develop in the myocardium even in an asymptomatic state after the disease recovers. LVEF, one of the most commonly used conventional parameters in the clinic, is not sufficient to detect these sequelae. LV-GLS is within the normal range, which prevents it from being used to screen for sequelae. Myocardial work parameters may be used to show detect long-term myocardial performance decrease and subclinical cardiac dysfunction.

Study Limitations

The study is a single-centre study. The study was conducted on a small group. Our results do not reflect acute COVID-19 patients. TTE results of patients before COVID-19 are not available. Evaluation of these results with multi-centre, larger studies may give more accurate results. Patients in the study were not followed up for a longer period of time, and research is needed to determine whether myocardial function improves or worsens in later years.

Conclusion

Significant reductions in GWI, GCW, and GWE were observed in fully recovered asymptomatic COVID-19 patients with pulmonary involvement, while GWW exhibited a significant increase. Although myocarditis does not develop during the course of COVID-19 disease, myocardial sequelae may remain after the disease recovers. Myocardial work parameters may be the useful echocardiographic parameters in determining these myocardial sequelae.

Ethical Approval: *This study was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Reference number: HNEAH-KAEK 2021/75-3301, dated 15.03.2021).*

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